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Rationale and Design of the 'MITOCARE' Study: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of TRO40303 for the Reduction of Reperfusion Injury in Patients Undergoing Percutaneous Coronary Intervention for Acute Myocardial Infarction

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Published in:
Cardiology

DOI:
[10.1159/000342981](https://doi.org/10.1159/000342981)

2012

[Link to publication](#)

Citation for published version (APA):

Atar, D., Abitbol, J.-L., Arheden, H., Berdeaux, A., Bonnet, J.-L., Carlsson, M., Clemmensen, P., Cuvier, V., Danchin, N., Dubois-Rande, J.-L., Engblom, H., Erlinge, D., Firat, H., Jensen, S. E., Halvorsen, S., Hansen, H. S., Heiberg, E., Larsen, A.-I., Le Corvoisier, P., ... Vicaut, E. (2012). Rationale and Design of the 'MITOCARE' Study: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of TRO40303 for the Reduction of Reperfusion Injury in Patients Undergoing Percutaneous Coronary Intervention for Acute Myocardial Infarction. *Cardiology*, 123(4), 201-207. <https://doi.org/10.1159/000342981>

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27

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Rationale and design of the “MITOCARE” study: a phase II, multicenter, randomized, double-blind, placebo controlled study to assess the safety and efficacy of TRO40303 for the reduction of reperfusion injury in patients undergoing percutaneous coronary intervention for acute myocardial infarction

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EudraCT number: 2010-024616-33

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Keywords

EU-FP7 grant; acute myocardial infarction; percutaneous coronary intervention; reperfusion injury; TRO40303

Abstract

Treatment of acute ST-elevation myocardial infarction (STEMI) by reperfusion using percutaneous coronary intervention (PCI) or thrombolysis has provided clinical benefits; however, it also induces considerable cell death. This process is called reperfusion injury. The continuing high rate of mortality and heart failure post-AMI emphasizes the need for improved strategies to limit reperfusion injury and improve clinical outcomes.

The objective of this study is to assess safety and efficacy of TRO40303 in limiting reperfusion injury in patients treated for STEMI. TRO40303 targets the mitochondrial permeability transition pore (mPTP), a promising target for the prevention of reperfusion injury. This multicenter, double-blind study will randomise patients with STEMI to TRO40303 or placebo administered just before balloon inflation or thromboaspiration during PCI. The co-primary efficacy measures will be infarct size expressed as plasma creatine kinase (CK) and troponin I area under the curve over three days. The main secondary endpoint will be infarct size normalized to the myocardium at risk, as expressed by the myocardial salvage index (MSI) assessed by cardiac magnetic resonance (CMR). The study is being financed under a EU-FP7 grant and conducted under the auspices of the MITOCARE research consortium, which includes experts from clinical and basic research centres, as well as commercial enterprises, throughout Europe.

Results from this study will contribute to a better understanding of the complex pathophysiology underlying myocardial injury post STEMI. The present paper describes the rationale, design and the methods of the trial.

Background

Current treatment of acute ST-elevation myocardial infarction (STEMI) by reperfusion using percutaneous coronary intervention (PCI) or thrombolysis provides tremendous clinical benefits by reducing infarct size and mortality following cardiac ischemia. However, reperfusion also induces considerable cell death. This process is called reperfusion injury and is believed to account for about 50% of the remaining infarction [1]. The continuing high rate of mortality (~10%) and heart failure after acute myocardial infarction (AMI) (~18%) [2], emphasizes the need for improved strategies to limit reperfusion injury in order to further improve clinical outcomes.

Several strategies for the reduction of reperfusion injury, such as post-conditioning [3], cyclosporine A [4], and FX06 [5], have been studied in phase II trials in patients undergoing PCI. Although these therapies have demonstrated the potential to reduce infarct size as measured by some cardiac parameters, results were not consistent for all biomarkers or cardiac magnetic resonance (CMR) measurements.

In the clinical trial with cyclosporine A, a significant 40% reduction of plasma creatine kinase (CK) area under the curve from 0 to 48 h (AUC_{0-48}) was observed together with a 20% reduction of infarct size as assessed by MRI [4]. However, the effect on plasma troponin I, which is considered a more specific marker for myocardial damage than CK, was not statistically significant. Similarly, FX06 resulted in a significant 58% reduction of the necrotic core zone as assessed by MRI, but no significant change in late gadolinium enhancement (LGE), mean troponin I plasma levels, or the CK-myocardial band (CK-MB) activity [5]. The efficacy of post-conditioning remains controversial despite positive results in early studies [3,6-10]. Subsequent

trials did not report a reduction in infarct size, but rather found that post-conditioning might have potential harmful effects [11,12].

TRO40303 (3,5-seco-4-nor-cholestan-5-one oxime-3-ol), a mitochondrial permeability transition pore (mPTP) modulator, was identified in a cell-based assay designed to identify molecules that maintain survival of trophic factor-deprived motor neurons [13]. It binds specifically to the mitochondrial translocator protein (TSPO) at the cholesterol site, and has the potential to decrease mitochondrial mediated cell death.

TRO40303 has been shown to reduce infarct size in preclinical animal models [14]. It specifically targets reperfusion-related events, delaying mPTP opening triggered by hypoxia reoxygenation in cardiomyocytes *in vitro*, and reducing the release of apoptosis-inducing factor (AIF) into the cytosol after *in vivo* ischemia reperfusion [14]. Since TRO40303 targets specific reperfusion events, it has the potential to prevent or limit myocardial reperfusion injury, evolution to heart failure, and the subsequent need for regenerative therapies.

The MITOCARE consortium, which began in January 2011, is a group of experts from 9 clinical centres, 3 basic research centres, and 4 small and medium-sized enterprises, for a total of 16 teams throughout Europe specializing in clinical and basic research, biomarkers, imaging, and informatics. This EU-7th Framework Programme (EU-FP7) funded consortium focuses its expertise on the problem of cardiac ischemia reperfusion injury.

Study Rationale

This trial seeks to evaluate the efficacy and safety of a new drug, TRO40303, in patients presenting early with a STEMI, the period when reperfusion therapy has the greatest benefit. TRO40303 targets the mPTP, a highly promising target for the prevention of reperfusion injury [15,16]. The primary outcome measure will be reduction in infarct size, which is known to be an important surrogate endpoint for morbidity and mortality following AMI [17,18].

In the present phase II trial, TRO40303 or placebo will be given, as an adjunct to current standard cardiac care, to patients undergoing primary PCI to treat a STEMI. Results from this study will contribute to a better understanding of the complex pathophysiology underlying myocardial injury post-STEMI.

Study Objectives

The objective of the study is to assess the safety and efficacy of TRO40303, administered just before balloon inflation or thromboaspiration during PCI, for the limitation of infarct size in patients treated for STEMI. Comparative efficacy between TRO40303 and placebo treated patients will be assessed using cardiac biomarkers and cardiac imaging. The co-primary measures of efficacy will be infarct size expressed as AUC for CK and AUC for troponin I (used for sample size calculation) over 3 days.

The main secondary outcome measure will be infarct size normalized to the myocardium at risk, expressed as “myocardial salvage index” (MSI) as evaluated by CMR. Additional secondary outcome measures to be compared between TRO40303 and placebo treated groups include: left ventricular function after PCI as measured by CMR (day 3-5) and echocardiography

(day 3-5 and day 30); ST-segment decrease after PCI (pre-PCI ECG compared to an ECG performed one hour post stenting); magnitude of microvascular obstruction as measured by CMR; and transmural extension of infarct as measured by CMR.

A subgroup analysis of infarct size, as evaluated by cardiac biomarkers and cardiac imaging, will be conducted according to the culprit vessel. In addition, patients will be classified according to Killip class and GRACE score.

Safety will be assessed at baseline, and at day 3 and day 30 after PCI. Measures include physical examination (clinical symptoms, weight), vital signs (blood pressure, heart rate), serum creatinine, triglycerides, urea, blood glucose, electrolytes, serum bilirubin, γ -glutamyltransferase, alkaline phosphatase, amino transferase (ASAT), alanine amino transferase (ALAT), and HDL/LDL cholesterol, as well as haematology and blood coagulation tests. Cumulative incidence of major adverse events occurring during the first 48 h after reperfusion, including death, heart failure, AMI, stroke, recurrent ischemia, the need for repeat revascularization, renal or hepatic, vascular complication, and bleeding will be assessed. Cardiac and non-cardiac events occurring within the initial 30 days will be recorded.

Additional biomarker measures are listed in Table 1. These markers will be used to assess factors for potential confounding influence or prognostic value for infarct size, future progression to heart failure, risk stratification, mechanism of cardioprotection and variability of response. Biomarker assays are centralized. In addition, a bio-bank of patients' plasma, serum, and RNA will be established for further investigations.

Study Design

MITOCARE is a prospective, multicenter, randomized, double-blind, placebo-controlled, phase IIa, proof-of-concept study in patients with large STEMI undergoing primary PCI, where TRO40303 or placebo will be administered as a single intravenous bolus prior to the reperfusion by angioplasty.

Patient Population

The study will be conducted in 9 study centres across 4 European countries. A planned total of 180 patients will be assigned 1:1 to receive either TRO40303 or placebo. The study population includes patients >18 years of age with a first-time AMI. Patient inclusion and exclusion criteria are listed in table 2.

Study Interventions

Eligible patients will undergo primary PCI and receive concomitant medications according to the current standard of care. After coronary angiography, but just before balloon inflation or thromboaspiration, patients who meet the enrolment criteria will be randomized to receive either placebo or TRO40303 (Figure 1). Randomization is ensured by taking the treatment units in ascending and consecutive order in each infarction stratum (anterior/posterior as determined on ECG).

Patients will receive an intravenous slow-bolus (35 mL/min) injection of TRO40303, 6 mg/kg, or an equivalent volume of placebo, a maximum of 15 minutes (ideally less than 5 minutes) before balloon inflation and stenting. Patients will subsequently undergo in- or outpatient CMR and echocardiography between day 3 (ideally) and 5. Follow-up safety

assessment and echocardiography will be performed at day 30 post-PCI. Patients will remain in hospital as long as medically indicated.

Since this clinical trial is being conducted within the context of an acute medical emergency, traditional case report forms will be replaced with a new electronic version (eCRF) available on portable devices (iPad™) and adapted for an emergency setting. This will allow for greater ease of data collection and reduce the possibility of errors in study monitoring.

Cardiac MRI

Cardiac imaging has been shown to allow for assessment of infarct size and heart function in acute ischemic heart disease [19]. Cardiac magnetic resonance using LGE is currently considered the clinical method of choice for detailed depiction of myocardial infarction [20,21]. Clinically, imaging techniques are not systematically applied, primarily due to cost limitations; however, they are very useful in establishing the efficacy of new cardio-protective agents.

Infarct size in man is influenced by the duration of ischemia and by the size of myocardium at risk [22], which is dependent on the site of coronary occlusion. Cardiac magnetic resonance has been shown to enable quantification of myocardium at risk using T2-weighted CMR [23]. This technique has also been clinically validated against myocardial perfusion single-photon emission computed tomography (SPECT) and shown to depict the myocardium at risk up to one week after the acute coronary event [24]. Furthermore, contrast-enhanced steady state free precession (SSFP) has recently been shown to also enable depiction of myocardium at risk one week after the acute event [25,26]. The main secondary endpoint in this study is the infarct size normalized to the myocardium at risk, expressed as the MSI. Use of this parameter measures the efficacy of treatment, but also provides data on patient variability and allows comparisons with preclinical data where infarct size is usually evaluated as the percentage of the area at risk.

Infarct size will be assessed from the LGE CMR images using a previously validated quantification method [27]. To avoid overestimation of infarct size by LGE CMR in the first days after the acute event [28,29], the CMR will be performed 3-5 days later. Myocardium at risk will be assessed either by T2-weighted imaging [24] or contrast-enhanced SSFP imaging [25]. All image analysis will be performed by ImaCor AB (Lund, Sweden). The CMR imaging will be performed on whole-body MR scanners with cardiac applications used for standard clinical CMR.

Statistical Considerations

The sample size calculation was based on a standardized difference of 0.47, estimated from data in the study by Piot et al. [4]. Assuming a reduction of 35% in troponin I AUC, for a statistical power of 85% and a probability of type I error of 0.05 using a two-sided test, the sample size was computed to be 166 patients (83 per group), which has been rounded to 180.

Between-group comparisons of AUCs for serum troponin I and CK release will be performed using O'Brien's method for multiple endpoints testing. Comparisons of CMR data will be performed using an analysis of covariance (ANCOVA) mixed model. Centre and patients will be considered as random effects and treatment as a fixed effect. Time to PCI, area at risk, and culprit artery will be used as covariates for these analyses. All analyses will be performed on the intent to treat (ITT) and per-protocol (PP) populations.

For the safety analyses, a comparison of the incidence of cumulative adverse clinical events between treatment groups will be performed using Fisher's exact tests.

Trial Organization

Steering Committee

The clinical research steering committee (CRSC) is responsible for supervising the trial and shall provide advice to the project coordinator (Trophos) pertaining to key decisions for the good management of the clinical trial. The CRSC will also bear overall responsibility for the design, conduct, and supervision of the study. It is responsible for reviewing the progress of the study at regular intervals to guarantee safety and trial integrity. The committee will also be responsible for providing clinical guidance on how to interpret the study protocol, study implementation, and elucidation of results.

Data Management & Statistical Analysis

All data management and statistical analysis related tasks will be conducted by the Clinical Research Unit, Lariboisière Hospital, Paris, France with the resultant outcome and safety data being continually provided to the independent drug safety monitoring firm. A new eCRF will be created by Mobile Health for use on the portable iPad™ device.

The CMR images will be transferred from the study centres to a central image database using a new software platform developed by the consortium. Images are automatically anonymised and scanned for inconsistencies before being electronically transferred. As soon as images are transferred, a quality assurance manager on-call is notified via text message. Images can be reviewed on any web-enabled mobile device, allowing for direct and fast feedback to sites regarding image quality and potential deviations from imaging protocol, thus potentially minimizing the risk of missing patient data due to inadequate imaging.

Data Monitoring Committee

Two clinicians and a methodologist will take part in a data monitoring committee, tasked with ensuring patient safety during the trial. The committee will regularly be provided with safety and efficacy data in a semi-blind way, as well as details of all serious adverse events.

Clinical Event Committee

The clinical events committee (CEC) is made up of interventional and non-interventional cardiologists who are not participants in the study. The CEC will be responsible for the adjudication of cardiovascular events based on review of CRF data, serious adverse event reports, source documents (hospital discharge summary, ECGs, and other supporting documents).

Safety and Ethics Monitoring Committee

The safety & ethics monitoring committee (SEMC) is in charge of ethics and personal data protection in the clinical trial. It is composed of a data protection specialist and an ethics specialist.

Clinical Implications

Previous data show that TRO40303 targets a key event that occurs at the time of reperfusion, namely the mPTP opening; making this agent a promising option in reducing reperfusion injury. The MITOCARE project aims to provide *in vivo* validation of mPTP as a relevant target for the prevention of myocardial ischemia reperfusion injury, and provide evidence that these mitochondrial processes are modifiable in humans. Effective reduction of reperfusion injury using TRO40303 should decrease the need for regenerative treatments, reduce the development of heart failure, and importantly, reduce mortality.

The MITOCARE project will help increase the understanding of the pathology and evolution of AMI, by identifying and extensively analyzing patient-related confounding factors. Identification of new biomarkers will enhance the subsequent development of better tools for the diagnosis and follow-up of AMI.

In addition, clinical results will be compared to those in preclinical models of AMI in order to better refine the understanding of these models, including their utility and limitations for use in research on the pathophysiology of reperfusion injury and for testing potential therapies.

Acknowledgement

The MITOCARE project is supported by the European Union under the 7th Framework Programme for RTD - Project MITOCARE - Grant Agreement HEALTH-2010-261034. One of the beneficiaries of this grant is Trophos SA, Marseille, France.

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Table 1. Additional biomarker measures

Cardiac function/vascular biomarkers	<ul style="list-style-type: none">• Troponin T, CK-MB: creatine phosphokinase-MB, N-terminal prohormone of brain natriuretic peptide, pro-adrenomedullin
Renal function biomarkers	<ul style="list-style-type: none">• Cystatin C, microalbuminuria
Inflammation biomarkers	<ul style="list-style-type: none">• C-reactive protein, interleukins 1b, 6, 10, immunoglobulins, tumour necrosis factor-alpha
MOA related biomarkers	<ul style="list-style-type: none">• Cytochrome C, oxidized LDL, myeloperoxidase
Diabetes biomarker	<ul style="list-style-type: none">• Haemoglobin A_{1c}
Platelet activation	<ul style="list-style-type: none">• Thromboxane in urine
Exploratory biomarkers	<ul style="list-style-type: none">• At least three exploratory biomarkers

LDL: low-density lipoprotein

Table 2. Inclusion and exclusion criteria

Inclusion criteria

- Age >18 years old
- Male and female with non child-bearing potential*
- First AMI defined as:
 - Nitrate resistant chest pain ≥ 30 min
 - New ST elevation at J-point in two contiguous leads with cut-off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2–V3 and/or ≥ 0.1 mV in other leads
- Presenting within 6 h of onset of chest pain
- Clinical decision to treat with PCI
- Occlusion of culprit artery with TIMI flow grade 0-1 at time of admission and before PCI
 - Occlusion affecting the following coronary arteries: left anterior descending artery, or dominant or balanced right coronary artery, or dominant or balanced left circumflex artery
- Signed informed consent to participate in trial before any study-related procedure or gave oral consent in France (patient should sign the ICF within 12 hours after procedure)

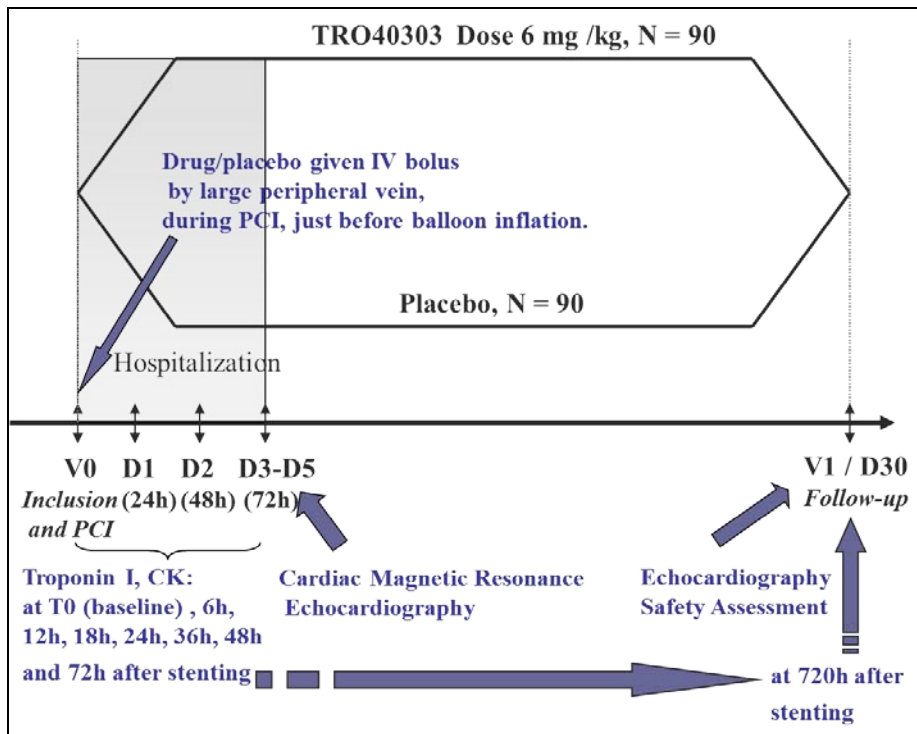
Exclusion criteria

- Cardiac arrest, ventricular fibrillation, cardiogenic shock, stent thrombosis, previous AMI, angina within 48 h before infarction, previous CABG, intravenous fibrinolytic therapy within 72 h prior to PCI
- Atrial fibrillation
- Pacemaker
- Concurrent inflammatory, infectious, or malignant disease
- Biliary obstruction or hepatic insufficiency
- History or presence of egg allergy

*Postmenopausal, ovariectomised or hysterectomised patients. Menopause defined as age >60 years, or between 45 and 60 years being amenorrhic for ≥ 2 years

AMI: acute myocardial infarction; TIMI: thrombolysis in myocardial infarction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; CMR: cardiac magnetic resonance

Figure 1. Study design



CK: creatine kinase